Remarks

This response is to the final Office Action mailed September 24, 2009.

Claims 35-38, 41, 50, 55-58, 61, 63 and 80 are currently pending and at issue in this application. Claims 22, 25-27, 29, 42, 46-49, 51-54, 59-60, 62 and 64-68 are currently withdrawn from consideration. Claims 22, 35-38 and 80 are amended. Claims 22 and 35-37 have been amended to correct dependencies. Support for the amendments to claims 38 and 80 can be found throughout the specification, for example at Paragraphs 1, 7 and 35 of the application as filed. Claims 78 and 79 are cancelled. Claims 1-21, 23-24, 28, 30-34, 39-40, 43-45 and 69-77 were cancelled previously.

This amendment also incorporates remarks made during the telephonic interview with the examiner on November 10, 2009 ("Interview").

Claim Rejection Based on Section 112

In the Office Action at page 2, claims 22, 35-37 and 80 are rejected under Section 112, second paragraph. The Examiner correctly notes that claims 22 and 35-37 should be dependent on claim 38. Applicants have amended claims 22 and 35-37 to reflect this fact.

The Examiner also claims that claim 80 is vague regarding the meaning of "regulating body weight" because the term is used twice in the first element of the claim. Applicants respectfully traverse. However, solely to expedite prosecution, and per the Examiner's suggestion as communicated during the Interview, Applicants have amended the claims to clarify the meaning of

claim 80. Applicants have replaced the second use of "regulating body weight" with "in need thereof."

Furthermore, the Office Action rejects claim 80 under Section 112, paragraph 1, alleging that claim 80 does not have support for the element "two antagonists." Applicants respectfully traverse. However, solely to expedite prosecution, Applicants have amended the claim so that it reads as "antagonists." For example, paragraph 35 of the application as filed provides support for the use of antagonists in the invention.

With these changes, Applicants respectfully submit that the rejections under Section 112 are overcome and the application is now ready to issue.

Claims Rejections Based on Section 103(a)

Rejection Based on Norman in view of Xue

In the Office Action at page 5, claims 38, 41, 50, 55-58, 61-63 and 80 are rejected under 35 USC 103(a) as unpatentable over U.S. Patent Number 6103709, to Norman, in view of Xue, *The* Agouti *Gene Products Inhibits Lipolysis in Human Adipocytes via a* Ca^{2+}*-Dependent Mechanism,* FASEB J, vol. 12, p. 1391-1396, Oct 1998. Applicants respectfully disagree. The references, whether considered alone or in combination, do not disclose or suggest the claimed methods. Furthermore, a number of significant differences exist between the Norman invention and the research by Xue that would prevent the combination of these two references by a person of ordinary skill.

Norman claims the use of Vitamin D metabolites to treat Vitamin D related diseases. Norman describes the effect of

Vitamin D metabolites, such as 1α, 25-dihydroxyvitamin D_3, on three cell types: osteoblasts, osteoclasts and intestinal epithelial cells. 1α, 25-dihydroxyvitamin D_3 affects each cell differently. Also, according to the present invention, it affects adipocytes in even another way.

Because the affect of 1α, 25-dihydroxyvitamin D_3 is different in each cell type, the effect of 1α, 25-dihydroxyvitamin D_3 on any given cell can not be predicted without experimentation. Thus the research by Norman is of no use in predicting the outcome of experiments involving Vitamin D metabolites on other cells.

According to the claimed invention, when an adipocyte is exposed to 1α, 25-dihydroxyvitamin D_3, the adipocytes will absorb calcium, thereby increasing the calcium concentration within the cell and leading to weight loss and/or increased metabolism. None of Norman's three cell types respond to 1α, 25-dihydroxyvitamin D_3 in this way. In fact, intestinal epithelial cells respond in the opposite way, with 1α, 25-dihydroxyvitamin D_3 causing a decrease in intracellular calcium concentrations.

Norman describes transcaltachia, the movement of calcium through an intestinal epithelial cell. In column 12, Norman summarizes transcaltachia as the process by which calcium moves through an intestinal cell, and into the body, lines 51 to 54. Both column 12 and column 21 describe a rapid response mediated by VDR_{mem} receptors. Column 21 details how intestinal epithelial cells use exocytosis to maintain a concentration gradient within the cell, encouraging calcium in the intestinal lumen to enter the cell, so that this calcium can be exported to the bloodstream. 1α, 25-dihydroxyvitamin D_3 in the 6-s-cis shape is the signal that the VDR_{mem} receptors receive to export the

calcium from the intestinal epithelial cell into the bloodstream. From column 21, line 33 to column 22, line 5, Norman describes the specific biochemical pathway used by an intestinal epithelial cell to signal the export of calcium by 1α, 25-dihydroxyvitamin D_3. Norman divides the process of transcaltachia into three steps. In step 1, column 21, lines 34-39, a calcium rich food is ingested by the body and enters the intestinal lumen, and the calcium moves into the interior of the intestinal epithelial cell. Next, in step 2, the calcium is collected into vesicles, as detailed in lines 39-44. Then, in step 3, calcium export is initiated using active exocytosis, triggered by 1α, 25-dihydroxyvitamin D_3, as described in lines 44 to 56. The next paragraph, starting at line 57, further explains the interaction between 1α, 25-dihydroxyvitamin D_3 and the VDR_{mem} receptor to generate this signal to begin the exit of calcium out of the intestinal epithelial cell and into the blood stream. Norman even notes, in column 22, lines 2 to 5 that the purpose of this process is to make calcium from food available for delivery to the bones by the blood stream.

When Norman investigated transcaltachia, he tested the concentration of calcium in the blood stream to measure the level of transcaltachia in the organism. He did not measure the calcium concentration within the intestinal epithelial cell. Both Examples 3 and 5 describe experiments using baby chicks to measure the influence of 1α, 25-dihydroxyvitamin D_3 on transcaltachia. In each experiment, Norman measures the starting calcium concentration in the blood. He then places 1α, 25-dihydroxyvitamin D_3 in the body of the chick, and calcium in the chick's intestinal lumen. Finally, he collects a blood sample from the chick and measures the calcium concentration of the

blood. Norman's research method suggests that he did not expect the calcium concentration of the intestinal epithelial cell to increase for a sustained or measurable period of time. In contrast, he expected the 1α, 25-dihydroxyvitamin D_3 to cause the cell to export calcium into the bloodstream where Norman could measure it.

On the other hand, according to the claimed methods, Vitamin D metabolites will cause an increase in intracellular calcium in adipocytes. This is distinct from the effect that 1α, 25-dihydroxyvitamin D_3 has on an intestinal epithelial cell. Thus a person skilled in the art could not use Norman's research on intestinal epithelial cells to predict that an adipocyte would absorb calcium when exposed to 1α, 25-dihydroxyvitamin D_3. This absorption of calcium in adipocytes is unpredictable.

Furthermore, Zemel discovered that blocking calcitrophic hormone activity in adipocytes with Vitamin D metabolites leads to weight loss and/or increased metabolism. Adipocytes absorb calcium, and retain that calcium to produce an increase in intracellular calcium concentration. None of the three cells Norman studied retain calcium. As explained above, intestinal epithelial cells export calcium when exposed to 1α, 25-dihydroxyvitamin D_3. This results in a decrease in calcium concentration. Norman also studies osteoblasts and osteoclasts. These two bone cells both temporarily absorb calcium when exposed to 1α, 25-dihydroxyvitamin D_3, but they immediately export that calcium to a new location. Osteoblasts absorb calcium from the blood and deposit it onto the bone to produce calcified bone matrix. Osteoclasts reverse this process by "reabsorbing" the calcium from the bone and depositing it into

the blood stream for use in other parts of the body, as explained in column 19, lines 40 to 48.

Norman describes cells that 1α, 25-dihydroxyvitamin D_3 induces to export calcium or import calcium only temporarily. The effects of 1α, 25-dihydroxyvitamin D_3 are so varied that a person skilled in the art could not pick a cell and know what effect, if any, 1α, 25-dihydroxyvitamin D_3 will have on that cell. The effect of 1α, 25-dihydroxyvitamin D_3 on any cell is unpredictable. Thus Norman cannot be used as the basis for a 103 obviousness rejection.

The Examiner also cites Xue, in combination with Norman. However, nothing in Xue would indicate to a person skilled in the art that Xue could be combined with Norman. Xue does not study, or mention, 1α, 25-dihydroxyvitamin D_3 or any other Vitamin D metabolite. Xue does not study, or mention, osteoblasts, osteoclasts, or intestinal epithelial cells. Xue relates to a disease that is not included in the extensive list of diseases that Norman claims his invention could treat, as listed in column 4, lines 21 to 37 of Norman. Given the extensive and diverse list of diseases that Norman claims can be treated, the fact that obesity is not included suggests that Norman did not think 1α, 25-dihydroxyvitamin D_3 could treat obesity. Nothing about Xue hints at any relevant factor of the Norman invention. There is no suggestion to combine these references, and a person skilled in the art would not try.

For these reasons, Applicants respectfully request that the examiner withdraw the Final Rejection and allow these claims.

Rejection based on Norman, Xue and Jequier

In the Office Action at page 10, claims 35-37 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Norman and Xue and further in view of Jequier (Am. J. Clin. Nutr. 1987).

In light of the arguments and amendments and amendments set forth above, Applicants respectfully submit that this rejection is now moot.

Rejection based on Science Daily, Summerbell and Jequier

In the Office Action at page 17, claims 35-38, 50, 55-58, 61-63 and 79 are rejected under 35 U.S.C. § 103(a) as being unpatentable over *Study: Calcium May Curb Weight Gain in Young Women*, http://www.sciencedaily.com/releases/19991014199042107.htm, April 21 1999 (hereinafter "Science Daily"), Summerbell, et al, *Randomized Controlled Trial of Novel, Simple and Well Supervised Weight Reducing Diet in Outpatients*, BMJ 1998, 317: 1487-9 (hereinafter "Summerbell") and Jequier.

In light of the arguments and amendments and amendments set forth above, Applicants respectfully submit that this rejection is now moot.

Rejection Based no Science Daily in view of Summerbell, Jequier and Peterson

In the Office Action at page 20, claim 78 is rejected under 35 USC 103(a) as being unpatentable over Science Daily in view of Summerbell and Jequier, and in further view of Peterson, Journal of Nutrition, 1992.

In light of the arguments and amendments and amendments set forth above, Applicants respectfully submit that this rejection is now moot.

Conclusion

For at least the above reasons, Applicants submit that the specification and claims are now in proper form, and that the claims are patentable over the prior art. Therefore Applicants submit that this application is now in condition for allowance.

Conditional Request For Constructive Assistance

Applicants have amended the claims of this application so that they are proper, definite and define novel and nonobvious structure. If for any reason this application is not believed to be in full condition for allowance, Applicants respectfully request the constructive assistance and suggestions of the Examiner pursuant to M.P.E.P § 2173.02 and § 707.07(j) in order that the undersigned can place this application in allowable condition as soon as possible and without the need for further proceedings.

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Respectfully submitted,

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